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A role for circuit homeostasis in adult neurogenesis

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Insertion of new neurons into adult neural circuits could either promote or impair circuit function, depending on whether homeostatic mechanisms are in place to regulate the resulting changes in neural activity. In the hippocampus (a mammalian forebrain structure important in aspects of memory and mood) several lines of behavioral evidence suggest important adaptive roles for adult-generated neurons, indicating that there could be mechanisms to control the potentially adverse increase in excitation associated with new cells. Here, we delineate behavioral and computational models for the role of circuit homeostasis in enabling neuron insertion to modulate hippocampal function adaptively, and we describe molecular and cellular mechanisms for implementing this circuit-level adaptive regulation of hippocampal activity.

Introduction

It is well established that the dentate gyrus of the hippocampus is a site of neurogenesis in the adult mammal, but experimental [1–4] and theoretical [5–12] explorations of the functional significance of this process are just beginning to emerge. It is often suggested that ongoing neurogenesis could be beneficial or essential to normal hippocampal function [1–12]; indeed, simple neural network models confirm that larger neural networks have larger memory storage capacity and are also more stable in the setting of decay mechanisms such as cell or synapse loss [6,13] (R. Yabaluri and K. Deisseroth, unpublished).

However, it is crucial to realize that adding excitatory neurons could result in serious maladaptive outcomes for hippocampal circuit function. One possibility would be epileptiform processes, because the sprouting of mossy fibers (powerful excitatory connections between the dentate gyrus and the downstream hippocampal layer CA3) has been linked to seizure activity [14,15]. In addition to their projection to CA3, dentate neurons form highly recurrent networks within the dentate, and an excess of mossy fiber excitation can result in seizure activity. Any new mossy fibers accompanying newborn granule cells could theoretically have a similar effect [16].

Second, beyond this potential pathological consequence of neurogenesis, physiological memory handling also could be adversely affected by the introduction of new neurons. Each new excitatory neuron adds excitatory drive between the dentate gyrus inputs and outputs; without compensation, this might increase the probability that downstream neurons will fire as a result of a given pattern of input to the hippocampus. If the fidelity of a given memory depends on activation of a precise pool of hippocampal neurons, memory recall could be impaired owing to the erroneous recruitment of output cells. Indeed, experimental data in animals with decreased neurogenesis suggest that recall of older memories is benefited when neurogenesis is reduced [3].

Yet despite these theoretical pitfalls, we and other mammals do not appear to suffer from adult neurogenesis. Seizure risk does not typically increase over the lifetime of humans or other mammals that exhibit adult neurogenesis, and radiation treatments that ablate neurogenesis [17] result in cognitive decline rather than enhancement in humans [18,19]. Indeed, animal studies that specifically provide moderate mid-cranial irradiation to target the hippocampus also result in cognitive damage, perhaps suggesting an important role for adult neurogenesis in normal cognitive function [1,2]. What mechanisms might be in place to prevent maladaptive consequences of neurogenesis?

One possible solution is that the dentate gyrus need not actually grow over life at all, as might be the case in humans [19] and some breeds of laboratory rodents [20]. Instead, each insertion of a newborn neuron could be balanced homeostatically by death of a pre-existing neuron. Recent theoretical models have included tests of this ‘turnover homeostasis’ model and found that such a mechanism does reduce the rate of spurious activation of neurons (false positives) by restraining the increase in excitatory drive during memory recall [5,6,11], enabling a net beneficial effect of the pool of newborn neurons on recall of the newest memories in highly active networks [5]. But for older memories, this turnover homeostasis mechanism also gradually increases the rate of failed activation of neurons (false negatives), because some of the neurons essential to the previously stored older memories are lost. False negatives for older memories might not be problematic for the hippocampus, because the importance of the hippocampus for memory recall appears to diminish for older memories [21–23] (but see [24]).

An alternative homeostatic mechanism could be implemented by fixing the activity level in the downstream neurons (e.g. CA3 pyramidal cells) regardless of

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how many dentate neurons are sending in activity or how potent the activity is. Various mechanisms, from the level of single channels to circuit responses, could keep CA3 activity relatively constant in the face of increasing excitation. For example, CA3 and granule cells could decrease their intrinsic excitability [25–28] or globally decrease expression of glutamate receptors across all synapses [28–31] to make themselves less responsive to the increasing excitatory inputs from the new mossy fibers.

Still other potential homeostatic mechanisms might operate at the level of the entire circuit, rather than in single cells. The new excitatory cells in the dentate could project strongly to inhibitory local circuits, or could be accompanied by a proportional increase in numbers of newborn inhibitory interneurons [32]; indeed, some excitatory granule cells could even take on an inhibitory GABAergic phenotype [33]. This is seen in younger neurons and in response to hippocampal seizures [34–36], although it remains unclear whether the net effect of this response is to increase or decrease levels of excitation within the hippocampus [37].

Any one of these mechanisms in principle might be employed by the hippocampus to compensate for increased excitatory drive from the dentate gyrus. Indeed, as illustrated by a MATLAB network model

Box 1. Circuit homeostasis selectively favors new memories in the setting of hippocampal neurogenesis

To assess effects of neurogenesis on memory storage, several groups have developed computational layered networks, typically representing hippocampal subfields including the entorhinal cortex (EC), dentate gyrus (DG) and CA3 [5,6,12]. In our current MATLAB implementation, the model network employs feedforward, full synaptic connectivity in three layers. As noted in the figure legend, this very simple network is not intended to model the hippocampus but rather to guide intuition on possible interactions of neurogenesis and homeostasis. Synaptic connections are excitatory, and neurons are represented as simple threshold elements with binary activation values ($\xi=0$ or 1). In this model (Figure Ia), each memory consists of randomly chosen active neurons (5% of the neurons are active in the EC, 2% in the DG and 5% in CA3, befitting the relative sparseness of dentate encoding [6,12]). Active neurons are represented here as filled circles, and inactive neurons as open circles. The model network (with each layer initially consisting of 500 neurons) learns 20 new memories per time step on the *x*-axis (Figure Ib) by adjusting the synaptic weights J between neurons using the standard Hebb rule $J_{ij}=\Sigma(\xi_i\times\xi_j)$, summed over all stored patterns. This is similar to the associative synaptic plasticity mechanisms that operate in the hippocampus (i.e. neurons that tend to be active together will have a stronger excitatory synaptic connection between them [5]).

The network is tested for recall of each learned pattern of activity (Figure Ia,i) by receiving as input just the first layer of each learned pattern (Figure Ia,ii); activity propagates through the network and accurate generation of the output layer is assessed (Figure Ia,iii). As described fully in [5], a cell j is determined to be active in the reconstructed memory if the incoming activity $\Sigma(\xi_i\times J_{ij})$ summed over all presynaptic neurons i into that cell exceeds the threshold $\theta_j=\alpha_i\times n_i$, where n_i is the total number of neurons in the $j-1$ layer and α_i is the fraction of active neurons in the $j-1$ layer. The total number of errors (error indicated by * for this example) defines the Hamming distance metric. (The network details are reproduced, with permission, from [5].)

Two types of error can be observed: false positives, in which incorrect units in CA3 are recruited, and false negatives, in which a given unit in CA3 fails to respond appropriately (indicated by *). Together, such errors could contribute either to forgetting (e.g. failure to remember the capital of New Jersey) or to improper associations (e.g. improperly recalling the capital of New Jersey as Sacramento). For display here, false positives and false negatives are combined into a single measure termed the Hamming distance. Low Hamming distances reflect accurate information recall, minimizing both false positives and false negatives.

The plots in Figure I(b) quantify fidelity of memory recall either in a stable (unchanging) network (Figure Ib,i) or in networks that incorporate neurogenesis alone (Figure Ib,ii), with homeostatic compensatory cell death (Figure Ib,iii) or with homeostatic regulation of activity (Figure Ib,iv). In the stable network (Figure Ib,i), the DG layer does not undergo neurogenesis, but as in all four panels the network still learns 20 new memories every time step. As the network learns more memories, the recall of both new and old memories becomes equally prone to error (chiefly false positives) because the network becomes overloaded and overactive. The output neurons of CA3 receive stronger inputs from the DG with each cycle owing to ongoing learning and synaptic strengthening, making it more likely that a CA3 neuron not involved in the original encoding of a memory will reach threshold and fire when that memory is replayed. This effect is equally deleterious to newer memories (high group number on the *y*-axis) and older (low group number) memories.

Neurogenesis is incorporated into the model by adding 25 new neurons only to the DG layer in each cycle, increasing the size of the DG to 1000 neurons by the end of the 20th cycle. When neurogenesis is added in this way (Figure Ib,ii), memory handling is even more impaired than in the stable case. This is due to an accelerated increase in false positives as the newborn neurons integrate into the circuit. Every new neuron added will create connections that have no bearing on previous patterns learned by the network, thus recruiting improper CA3 neurons during the recall of older memories. This model indicates that neurogenesis without homeostasis, rather than promoting memory stability, in fact can promote memory degradation or forgetting.

Whether or not this is a maladaptive effect of neurogenesis (perhaps the hippocampus must forget or clear old memories), the effect can be alleviated with turnover homeostasis or activity homeostasis. In the turnover homeostasis model (Figure Ib,iii), 25 DG neurons 'die' each cycle and are replaced with new neurons whose synaptic connections are initially zero (until they become involved with storing the next set of new memories, a biologically plausible arrangement). Here, there is a strong decrease in older memory fidelity, largely due to false negatives resulting from the death of neurons that were crucial to the old memories. Nonetheless, there is a clear benefit to short-term recall of the newest memories (along the diagonal) especially at high memory loads (later time points), because spurious activation of CA3 is restrained (fewer false positives occur because mean synaptic efficacy is lower in the presence of a newborn neuron pool replacing mature neurons).

But the greatest increase in memory stability is observed when neurogenesis is coupled to homeostatic mechanisms that restrict excitability in CA3 (Figure Ib,iv). Here, although neurogenesis increases network size and the level of excitatory input a given CA3 neuron receives, the fraction of active CA3 neurons is forced to remain constant at 5%. This requirement could be achieved in biologically plausible fashion by any of the activity-homeostatic mechanisms described in the main text, effectively eliminating the massive increase in false positives seen when no homeostasis occurs. In this situation, the stored memories are very stable even at high memory loads.

In summary, neurogenesis can promote memory stability so long as there is a homeostatic mechanism for controlling circuit activity. An interesting trend is that only in homeostatic conditions (Figure Ib,iii and Figure Ib,iv), new memories tend to be recalled more accurately than old memories, consistent with the widely held view that the hippocampus becomes progressively less important for recall of memories as they become more remote. Therefore homeostatic mechanisms are likely to favor stability of new memories in the setting of hippocampal neurogenesis, consistent with experimental evidence and many models of hippocampal function.

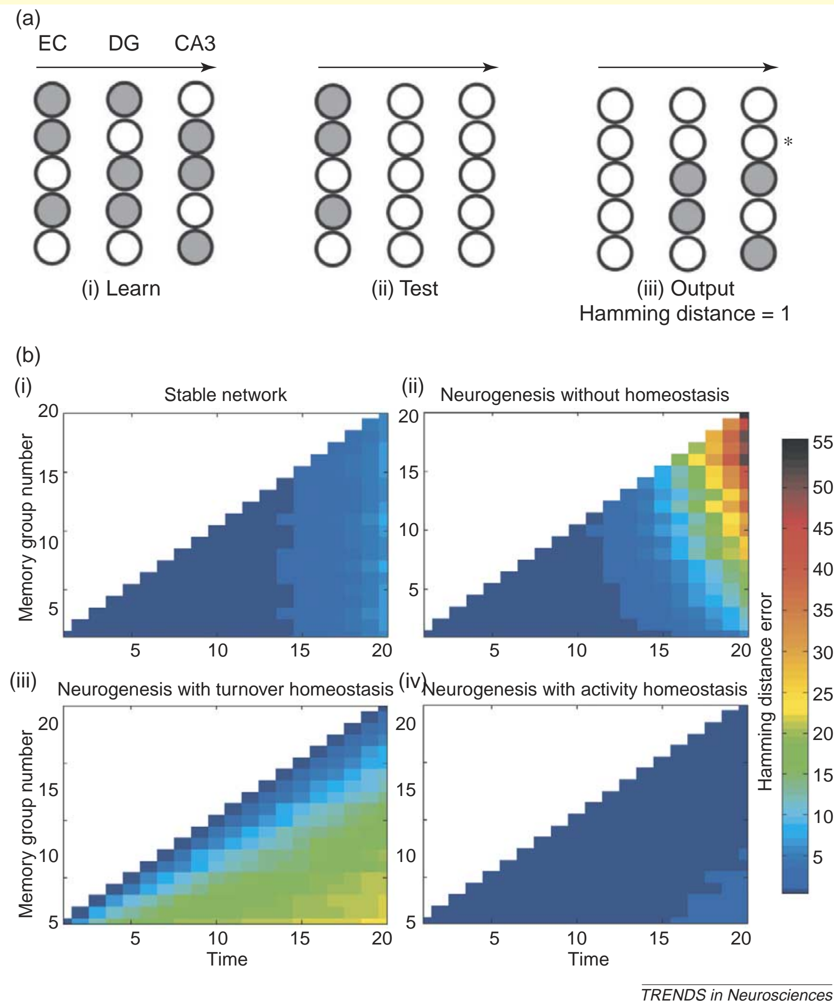

Figure I. Circuit homeostasis favors new memories in the setting of hippocampal neurogenesis. **(a)** Schematic of MATLAB implementation of the associative neural network model described in the box text. This simple network is not intended to model the hippocampus but rather to give an idea of possible interactions between neurogenesis and homeostasis in information storage. Input neurons in the first layer (analogous to the entorhinal cortex, EC) form connections with an internal layer (analogous to the dentate gyrus, DG), which connects to the output layer (analogous to CA3). Shaded circles are active neurons. The network is tested for recall of each learned pattern of activity (i), by receiving as input just the first layer of each learned pattern (ii); activity propagates through the network and accurate generation of the output layer activity pattern is assessed (iii). The total number of output layer errors (error indicated by * for this example) defines the Hamming distance. Adapted, with permission, from [5]. **(b)** Error (Hamming distance) as a function of time in a stable network (i), or in networks that incorporate neurogenesis alone (ii), neurogenesis with homeostatic compensatory cell death (iii), or neurogenesis with homeostatic regulation of activity (iv).

(Box 1), activity homeostasis works at least as well as turnover homeostasis in reducing the overall error rate caused by neurogenesis. The rate of false positives is greatly reduced, particularly in newer memories. Importantly, the ensuing benefits of neurogenesis are greatest in heavily loaded networks regardless of which homeostatic mechanism is used, implying that in episodes of extensive hippocampal activity, it would be advantageous for the circuit to increase the rate of new neuron production [5] (for review, see [38]). This predicted effect has been demonstrated both in culture [5] and in intact animals [2,5,39,40].

Models are valuable up to a point, but what do experimental results tell us about the cognitive utility or deleterious effects of adult neurogenesis? We will next detail recent experimental evidence on the role of neurogenesis in the context of proposed homeostatic mechanisms in the hippocampus.

Experimental evidence: neurogenesis and memory

Several groups [1–3] have tested cognitive consequences of ablating adult neurogenesis, by inhibiting the capacity of the native stem cell population to produce neurons. For example, Rola *et al.* and Snyder *et al.* have recently demonstrated that reduction of neurogenesis in young rodents leads to deficits in spatial memory task performance later in life [1,2]. Specifically, Snyder *et al.* [1] explored how irradiation in rats, leading to loss of newborn dentate neurons, affects spatial memory retention in the Morris water maze (Figure 1). Rats were irradiated at 40 days of age, trained in this hippocampus-dependent spatial memory task at ~70 days, and tested for memory retention at 90–110 days. Therefore, these animals spent nearly half of their lives without generating newborn neurons. Importantly, the delay of approximately one month between irradiation and behavioral training should be sufficient to give newborn neurons the opportunity to wire up in

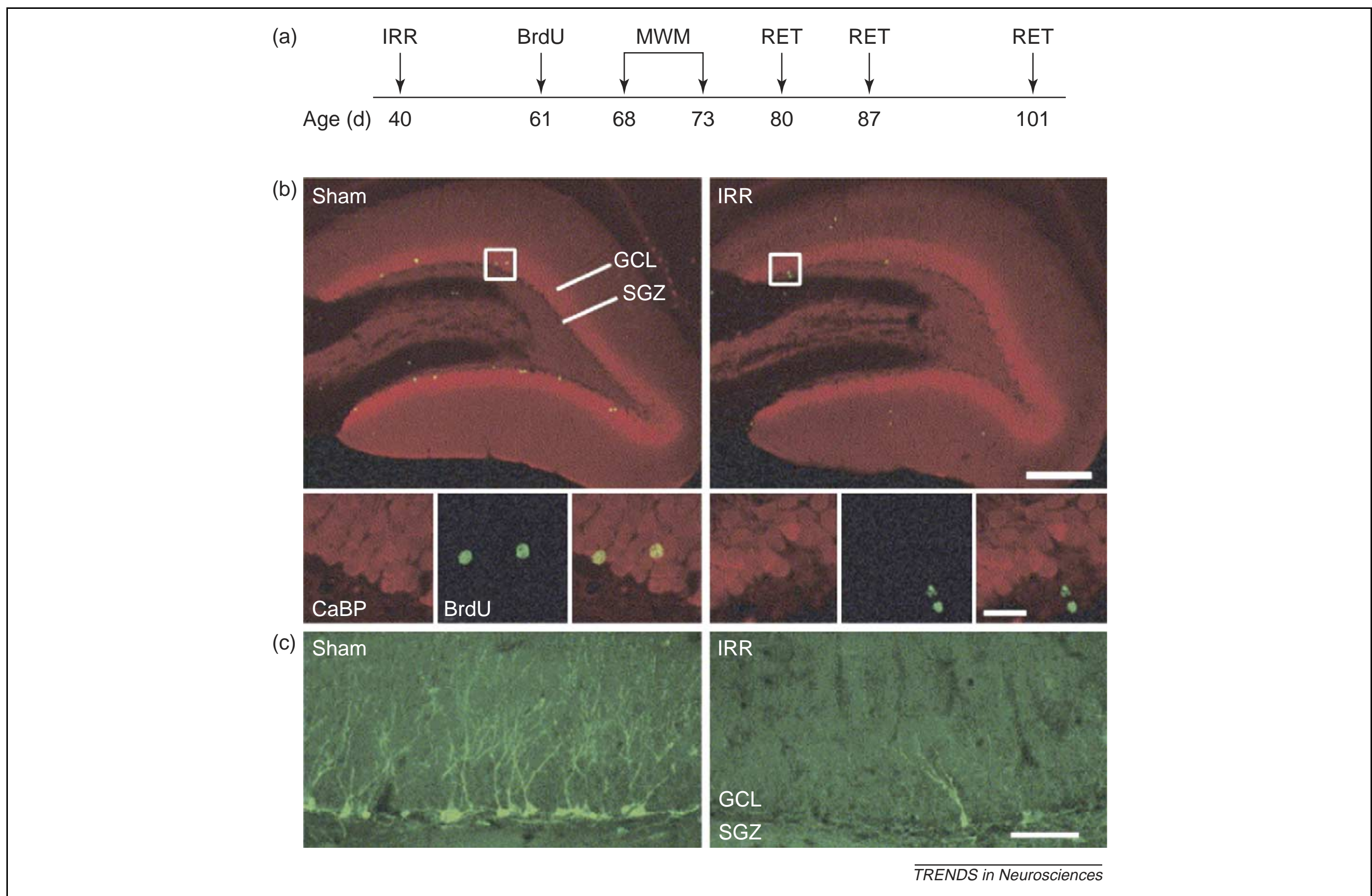

Figure 1. Irradiation permanently impairs the capacity of the native hippocampal stem cell population to produce neurons. **(a)** Time course of an experiment assessing effects of irradiation-induced prevention of neurogenesis on memory retention in the Morris water maze. Forty-day-old male Long Evans rats were irradiated (IRR) or sham-irradiated and subsequently trained and tested on the Morris water maze (MWM). Rats received a single bromodeoxyuridine (BrdU) injection one week before training to label dividing cells. Memory retention was tested at three subsequent time-points (RET). **(b)** Following behavioral testing, animals were sacrificed and brains were immunostained for BrdU (green) and the neuronal marker calbindin (CaBP; red). Irradiated hippocampi, in which neurogenesis was prevented, lacked BrdU–CaBP colabeling. Scale bar, 200 μm for whole dentate gyrus pictures, 30 μm for close-ups. **(c)** Lack of neurogenesis in irradiated animals is further illustrated by immunostaining for doublecortin, which labels immature neurons. Doublecortin-positive cells are abundant in sham-irradiated animals but rare or absent in irradiated hippocampi. Scale bar, 100 μm. Additional abbreviations: GCL, granule cell layer; SGZ, subgranular zone. Adapted, with permission, from [1].

the existing circuitry and to enable group differences to be seen with this study design [41–43]. Newborn neurons are especially plastic [41–45], and the irradiated animals had far fewer new, plastic neurons available for memory encoding at the time of training, perhaps resulting in a smaller effective memory-storage network and consequent reduced memory stability in the setting of physiological memory decay mechanisms, as already discussed.

However, owing to the permanent nature of the radiation effect, there are effectively two manipulations at once: there are far fewer young, plastic neurons present during memory storage, presumably leading to less-robust storage of memories, and there are also far fewer additional newborn neurons coming 'online' during the 2–4-week post-training retention period. Intriguingly, this second effect should oppose the first, because the fewer disruptive new cells inserted into the network after training, the more stable the memories will be (Box 1). Which effect will win?

Snyder *et al.* [1] first observed that memories were indeed more stable in the non-irradiated animals (Figure 2a), but were well aware that irradiation was causing the two effects already noted and made a strong effort to disentangle the two effects using a key second test: irradiating only after training (two days later). This manipulation should eliminate the contaminating factor of altered plastic network size during training and could isolate the possible disruptive effects of newborn neurons (Figure 2b). Interestingly, in this second experiment the irradiated animals no longer demonstrated impaired memory [1], and in fact there was perhaps a trend towards better retention in the irradiated animals (Figure 2b). Specific improvement in memory retention is also observed at significant levels in mice with reduced neurogenesis due to a mutation in the *presenilin-1* gene [3] (Figure 2c). In those experiments, retention of older memories on the hippocampus-dependent contextual fear conditioning task was enhanced in the low-neurogenesis animals.

Together, these experiments suggest that neurogenesis over a certain period can interfere with memories stored prior to this period but simultaneously promote stability of memories stored after this period. This interesting effect is also predicted by models that incorporate homeostatic regulation along with hippocampal neurogenesis (Box 1), whereas non-homeostatic models show no selective

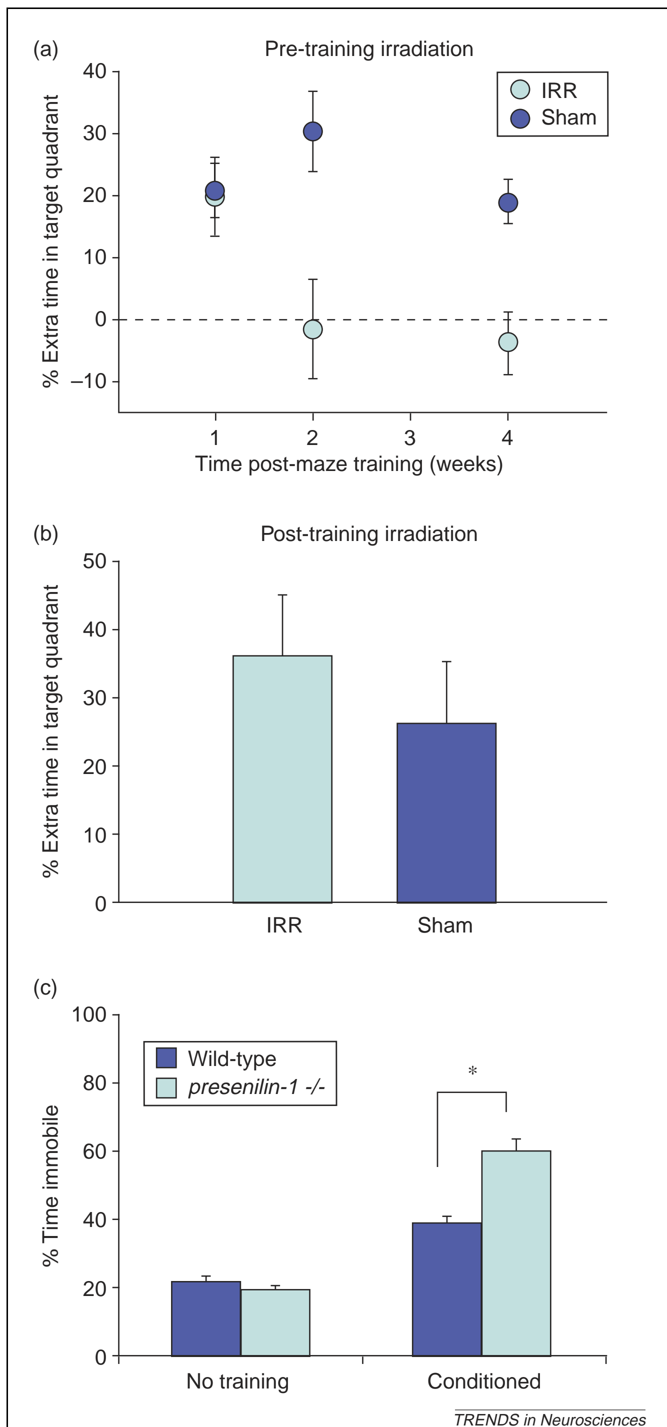

Figure 2. Complex effects of neurogenesis inhibition on long-term memory. **(a)** To assess the role of neurogenesis in spatial memory, male Long Evans rats were irradiated (IRR) or sham-irradiated four weeks before training on the Morris water maze spatial memory test. In this procedure, animals are trained to locate an escape platform in a circular pool based on spatial cues in a room. Following training, animals are tested for retention in a probe trial, where the platform is removed and the time an animal spends in the quadrant that originally contained the escape platform is scored. Memory was tested in a probe trial one, two or four weeks after training. Animals that spend extra time in the quadrant containing the escape platform during training are considered to have retained memory of the training. Irradiated animals that exhibit decreased neurogenesis fail to show preference for the target quadrant on the two-week or four-week probes. Preference at the one-week probe time point is unchanged by irradiation, probably because intrinsic memory decay mechanisms are not potent enough at this time to reveal stability changes associated with neurogenesis. We have not attempted to model in Box 1 what might be occurring within this one-week period after training. Notably, the animal is not trained to store new memories after initial training, in contrast to the ethologically plausible situation modeled in Box 1, in which memory storage is ongoing. **(b)** To determine whether neurogenesis following memory acquisition affects memory stability, animals were irradiated or sham-irradiated two days after training and tested three weeks later. No difference in probe performance was observed, although there is a trend towards better performance for the irradiated animals. **(c)** In agreement with this trend, mice with decreased neurogenesis due to a mutation in the *presenilin-1* gene have significantly enhanced retention of long-term contextual fear memory, which also depends on the hippocampus, relative to wild-type animals. Wild-type and mutant animals were reared in an enriched environment to increase neurogenesis and were trained on a contextual fear memory task, where an aversive shock is associated with a particular context. Two weeks after training, the animals were re-exposed to the conditioned environment, and memory retention was determined by the time spent motionless. *presenilin-1* mutants spend more time freezing than control animals (conditioned; * indicates $P<0.05$), whereas no difference is observed in animals that are not shocked in the same context (no training). No difference was observed in retention of a non-hippocampus-dependent cued fear memory task (data not shown). Adapted, with permission, from [1] (a,b) and [3] (c).

impairment of prior memories (Box 1). Therefore, both models and behavioral data appear to support the existence of homeostasis tuned to support neurogenesis.

Experimental evidence: homeostatic mechanisms

Do any of these homeostatic mechanisms really operate in the hippocampus in response to neurogenesis? We will now consider the experimental evidence for the homeostatic mechanisms already mentioned: (i) turnover homeostasis, (ii) intrinsic excitability regulation, (iii) synaptic scaling, (iv) neurogenesis of inhibitory interneurons, and (v) conversion of existing excitatory neurons to inhibitory neurons. We will discuss current evidence that supports or fails to support the role of each mechanism, and describe future experiments that could clarify the hypothesized role in each case.

Turnover homeostasis

Experimental evidence for neuronal turnover (cell death of mature neurons to compensate for insertion of new neurons) in the dentate gyrus is conflicting. Indeed, there is considerable controversy over whether the dentate gyrus grows during life. If neuron turnover were an important homeostatic mechanism, we would expect the dentate size to stay constant, as is perhaps the case in humans [19] and some breeds of rat [20]. However, in other rats [20] and in mice [40,46], the dentate appears to grow, suggesting a net gain of new neurons. Furthermore, were turnover homeostasis the primary mechanism of activity homeostasis, we would expect to see mature neuron death in the dentate that matches the rate of newborn neuron incorporation. Although apoptosis does occur in the dentate, most observed cell death is associated with newborn cells that fail to reach maturity [45,47]. To determine whether turnover homeostasis realistically operates in the hippocampus, future experiments should carefully determine whether the apoptotic rate of older neurons is quantitatively tuned to correlate with the rate of neurogenesis. In this context, it is interesting that strong bursts of activity can both be excitotoxic for mature neurons and promote newborn neuron formation [5], suggesting a specific mechanism for a quantitatively tunable form of turnover homeostasis.

Intrinsic excitability regulation

Intrinsic excitability regulation involves long-term changes in the number or activity of surface membrane

ion channels that stabilize firing rates during variable levels of excitatory input. Although frequently observed in cortical (e.g. sensory) neurons [25–27], homeostatic stabilization of intrinsic excitability has not been identified as clearly in the hippocampus. This might be due to the role of the hippocampus in temporary information storage; in contrast to primary sensory areas (where maintaining stability in firing rates might be essential to network function), enabling changes in hippocampal neuron excitability actually could be useful to store information temporarily. Indeed, in CA3 and CA1 of the hippocampus, some learning tasks do trigger increases in excitability [48]. If hippocampal neurons must actually increase excitability as a form of learning, excitability homeostatic mechanisms are unlikely to be the main homeostatic mechanism balancing the effects of hippocampal neurogenesis.

Synaptic scaling

Synaptic scaling refers to the process by which a neuron proportionally increases or decreases the synaptic expression of synaptic receptors (e.g. AMPA-type glutamate receptors) [29–31]. The net effect is to increase or decrease sensitivity to synaptic inputs across the whole neuron while preserving the relative strength of each synapse. Synaptic scaling is an especially attractive homeostatic mechanism for two reasons. First, because all synapses are modulated equally, the relative differences in synaptic strengths are maintained. Maintaining control over relative strengths between synapses is probably essential for memory storage in the hippocampus, which is thought to rely heavily on synapse-specific mechanisms of synaptic potentiation or depression. Second, synaptic scaling could provide a means by which older memories are removed from the hippocampus. As a CA3 cell reduces the overall number of AMPA receptors in its membrane, some of its relatively inactive synapses will lose enough receptors to become silent, eventually deleting the older memories. Thus, synaptic scaling in response to increased excitatory drive in the dentate gyrus might have the added benefit of clearing old memories in addition to facilitating the acquisition and consolidation of new information. Unlike intrinsic excitability homeostasis, synaptic scaling homeostasis might realistically operate widely in the hippocampus. It has been demonstrated that cultured CA3 neurons reduce expression of AMPA receptors throughout their surface membrane in response to prolonged excitatory input [31]. Future research should begin to explore whether synaptic scaling does indeed operate in the hippocampus *in vivo* and, if so, whether the changes in synaptic strength are quantitatively associated with the rate of neurogenesis.

Neurogenesis of inhibitory interneurons

Most models of the functional implications of neurogenesis, including that described in Box 1, assume that the newly generated neurons all become excitatory granule cells. However, it is possible that some of the newborn cells in fact take on an inhibitory phenotype. If the relative levels of inhibitory and excitatory neuron production are similar to those of the pre-existing neurons (or if newborn neurons were simply coupled strongly to inhibitory circuits), neurogenesis itself could be homeostatic, because the ratio of excitation to inhibition would be unchanged. Supporting this model, Liu *et al.* have suggested that ∼1/6 of newborn neurons in the dentate gyrus show features typical of GABAergic basket cells – interneurons that make inhibitory connections onto both dentate gyrus and CA3 neurons, and are in a good position to regulate both the dentate gyrus output and the responsiveness of CA3 to excitatory input [32]. Further research on the plausibility of this model should verify the existence of newborn inhibitory neurons, identify their patterns of connectivity, and determine whether the rate of inhibitory neuron insertion is tightly correlated with that of new excitatory neurons.

Conversion of pre-existing granule cells to the GABAergic phenotype

Another related mechanism of increasing inhibitory inputs to CA3 is the excitatory-to-inhibitory conversion of some mossy fiber synapses. Developing granule cells are both glutamatergic and GABAergic, and even into maturity the granule cells express low levels of both the inhibitory neurotransmitter GABA and the GABA-producing enzyme GAD [33,35,49]. During episodes of overexcitation, such as in a seizure or through the kindling of an acute slice, levels of GABA and GAD in the dentate gyrus dramatically increase, and resulting potent inhibitory synaptic events can be observed in CA3 [35,36]. The potential for granule cells to inhibit some targets in CA3 makes this mechanism an intriguing candidate for CA3 activity regulation. However, not all the synapses become GABAergic and, because the mossy fibers also synapse extensively onto inhibitory interneurons [50,51], there is disagreement as to whether this phenotype conversion results in a net increase or decrease in hippocampal excitation [37]. If the majority of converted (inhibitory) mossy fiber synapses form onto inhibitory interneurons, the expected effect is a net increase in spontaneous activity, which could potentiate seizures rather than alleviate them. To begin to address these possibilities in the context of physiological adult neurogenesis, it will be important to (i) study in detail the GABAergic phenotype and specific cellular projection targets of newborn neurons, and (ii) develop methods to study GABA-dependent neurogenesis-associated changes in circuit-level activity patterns within specific hippocampal subfields.

A final possibility is that none of these homeostatic mechanisms takes place because none are necessary *in vivo*; modest increases in network size might obviate the need for homeostatic mechanisms. But, because the dentate gyrus and CA3 possess robust recurrent excitation, a small increase in excitation resulting from neurogenesis could be sufficient to cause runaway excitation if no homeostatic controls are in place.

Summary

Promotion of memory stability associated with neurogenesis is most obvious when a homeostatic mechanism is in

place to stabilize the overall level of activity, and this principle is most important at higher activity levels or memory loads (Box 1). Furthermore, in homeostatic conditions associated with neurogenesis, new memories tend to be recalled more accurately than old memories (Box 1), consistent with the widely held view that the hippocampus becomes progressively less important for recall of memories as they become more remote.

Future research will need to explore expression of the several distinct forms of homeostatic plasticity in hippocampal neurons, with careful attention to the principle that the ideal homeostatic mechanism would be tightly linked to the rate of neurogenesis, which in turn is highly variable and exquisitely regulated. For example, treatments that increase the rate of neurogenesis, such as antidepressants, L-type Ca^{2+} channel agonists, an enriched environment or voluntary exercise [5,42,52–54], could enhance (directly or indirectly through the newborn neurons themselves) expression of homeostatic mechanisms.

Ultimately, understanding how the hippocampal network regulates itself in the face of changing activity from the dentate gyrus will strengthen our comprehension of the function of adult neurogenesis in memory storage. Bringing quantitative tools, network modeling and animal behavior to bear on this issue is also essential from the clinical and bioengineering standpoints. Because more neurons are not always better, as we move towards deriving therapeutic strategies and increasing control of stem cell behavior, it will be crucial to understand the quantitative consequences of our interventions at the network level.

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